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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/579,680	05/26/2000	Blake R. Pepinsky	BIIJ-P02-067	8259

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EXAMINER
O HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/17/2002

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/579,680	PEPINSKY ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *19,22-27,34,35,39,47,49,60,61 and 90-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,14,15,28-31,40-42,46,48,50,53,56,57,63-68,71,87-89 and 93-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *See Continuation Sheet* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17,18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims pending in the application are 1-10, 14, 15, 19, 22-31, 34, 35, 39-42, 46-50, 53, 56, 57, 60, 61, 63-68, 71 and 87-104 are .

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 1-10, 14, 15, 19, 22-31, 34, 35, 39-42, 46-50, 53, 56, 57, 60, 61, 63-68, 71 and 87-104 are .

DETAILED ACTION

1. Claims 1-10, 14, 15, 19, 22-31, 34, 35, 39-42, 46-50, 53, 56, 57, 60, 61, 63-68, 71 and 87-104 are pending in the instant application. Claims 1, 68, 87 and 89 have been amended and claim 62 has been canceled as requested by Applicant in Paper Number 16, filed Oct. 1, 2002.

Claims 19, 22-27, 34, 35, 39, 47, 49, 60, 61 and 90-92 are withdrawn as being drawn to a non-elected invention.

Claims 1-10, 14, 15, 28-31, 40-42, 46, 48, 50, 53, 56, 57, 63-68, 71, 87-89 and 93-104 are currently under examination.

Information Disclosure Statement

2. The IDS filed Nov. 4, 2002 (Paper No. 18) was a duplicate of the IDS filed Oct. 1, 2002 (Paper No. 17).

Priority

3. Applicants' amendment to the specification to recite the priority claimed to PCT/US98/25676 in the declaration is acknowledged, however, *the provisional applications must also be included in the statement.*

Withdrawn Objections and Rejections

4.1 The objection to the specification is withdrawn in view of Applicants' amendment.

4.2 The objection to claim 62 is withdrawn in view of Applicants' amendment.

4.3 The rejections of claims under 112 § 2 are withdrawn in view of Applicants' amendment.

Maintained Rejections

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, 14, 15, 28-31, 40-42, 46, 48, 50, 53, 56, 57, 63-68, 71, 87-89 and 93-104, which were provisionally rejected in the previous Office Action, are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 6, 10-18, 41-46, 48, 74, 77-79, 85 and 94-97 of U.S. Patent No. 6,444,793. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in Patent No. 6,444,793 are directed to hydrophobically modified hedgehog proteins (species), while the claims in the instant application are directed to hydrophobically modified proteins that bind a receptor (genus), and the genus is anticipated by the species.

It is acknowledged that Applicants on page 11 of the amendment state that they will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6.1 The rejection of claims 50, 53, 56, 57, 63-65, 68, 71, 87-89 and 93-104 are maintained under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for hedgehog proteins that are modified with lipophilic moieties and have increased activity and methods of making them, does not reasonably provide enablement for any other receptor or coreceptor binding protein also modified with lipophilic moieties that result in enhanced activity and methods of making them. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for reasons of record in the previous Office Action, Paper No. 14, at pages 6-8, and below.

Applicants traverse the rejection, and assert that the basis of the current rejection appears to be that the making and testing of other proteins modified using the methods of the present invention would involve undue experimentation, and it is with this contention with which Applicants disagree. Applicants cite M.P.E.P 2164.01 and *In re Wands* in support of their traversal, and submit that in the context of the present application, the state of the art and level of skill in the art is high, that basic techniques in molecular biology and chemistry are well known in the art, and that the specification also provides extensive guidance. Applicants also assert that in terms of working examples, the Examiner appears to agree that the present application provides working examples which indicate that the inventions works as Applicants allege, in

which Applicants show modification of various hedgehog proteins. Applicants also submit that an important criterion for evaluating undue experimentation is the amount of guidance provided by the specification, and cite *In re Colianni* and *In re Wands* in support of this. Applicants further assert that the specification provides extensive guidance as to methods of testing the polypeptides of the present invention to confirm that they meet the limitations of the claims, and provide the examples of testing the modified hedgehog proteins. Finally, Applicants submit that the consideration of Applicants' arguments and the determination of the enablement of the presently claimed invention should be evaluated separately for claims directed to the compositions and for claims directed to the methods of making the compositions.

Applicants' arguments have been fully considered but are not deemed persuasive. Each of Applicants' arguments will be addressed relative to the Wands Factors. There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

The Examiner agrees that the state of the art and level of skill in the art is high is, and that the techniques of making, hydrophobically modifying and purifying recombinant proteins are well known in the art. It would not require undue experimentation to make and test hydrophobically modified proteins, since these methods are well known in the art; however, the

quantity of experimentation is not the issue. The issue is that the claims recite the limitation that the modification enhances the protein's biological activity in the presence of the modification relative to the activity in the absence of the modification, and the protein binds to a receptor or coreceptor. This is the only aspect of the claims that is asserted to differ from the prior art. It is not predictable that any such modified protein would have enhanced biological activity. Applicants assert that the specification has provided a number of working examples which demonstrate that hedgehog proteins can be modified with any of a variety of different hydrophobic moieties using the methods of the invention to increase the potency and stability of the protein, and that the specification has provided extensive guidance as to methods of testing the polypeptides of the present invention to confirm that they meet the limitations of the claims. However, as discussed in the previous Office Action, the only working examples are of modified hedgehog proteins, which are a closely related family of proteins having similar structures and activities, and bind to structurally and functionally similar receptors, involved in developmental regulation, and which are naturally hydrophobically modified, and which natural hydrophobic modifications are required for activity. The soluble form of the N-terminal fragment of hedgehog lacking the cholesterol and palmitic acid is not as biologically active (about a 30-fold decrease in potency as compared to the lipid modified hedgehog, specification, page 3, lines 5-10). Even though the specification lists other extracellular signaling proteins that can be useful in the invention, there are no working examples other than hedgehog proteins. There is no evidence provided in the specification or in the prior art that any other signaling molecule is naturally modified with hydrophobic groups that are necessary for biological activity or that increase activity. The skilled artisan would find it credible that modifying a protein that is

naturally modified with hydrophobic moieties and as a result has enhanced activity, with different hydrophobic groups, would also find an enhancement in activity. But no evidence has been provided that modifying a protein with hydrophobic moieties that normally is not modified as such would increase the proteins activity. Therefore, the specification only provides one actual working example, that of the class of hedgehog proteins.

The MPEP states in section 2164.02:

> A single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled since at least that embodiment would be enabled. **However, a rejection stating that enablement is limited to a particular scope may be appropriate.** The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors. To make a valid rejection, **one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims.**

Although the level of skill in the art is high, neither the prior art nor the specification has taught that any extracellular signaling protein other than hedgehog proteins may be hydrophobically modified and have enhanced activity, and it is not predictable that any such modification on another other class of protein would have the same effect. Therefore, undue experimentation would be required to make and test any other extracellular signaling protein that would have enhanced biological activity.

All the Wands factors are considered and it is the balance of factors that determines whether a disclosure enables the use of the invention. In the previous Office Action, all of these factors were considered.

Finally, although Applicants submit that the consideration of Applicants' arguments and the determination of the enablement of the presently claimed invention should be evaluated

separately for claims directed to the compositions and for claims directed to the methods of making the compositions, the methods of making such modified proteins with enhanced activity are included in the rejection, because they have the limitation of enhancing the proteins' activity.

6.2 Claims 1-10, 14, 15, 28-31, 48, 66-67 and 93-104 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record in the previous Office Action, Paper No. 14, at pages 8-10.

Applicants traverse the rejection and submit that the evaluation of whether the claims satisfy the requirements under 35 U.S.C. 112, first paragraph, must be separately undertaken for claims directed to the composition and for claims directed to the methods. Applicants arguments are persuasive and the rejection over the methods is withdrawn. Applicants further traverse the rejection and assert that the analysis applied in the Office Action is inconsistent with the finding of the Court in the *Regents of the University of California v Eli Lilly & Co* case. Applicants submit that the pending claims define the claimed subject matter in terms of generic formulae that indicate with specificity what the generic claims encompass, and accordingly meet the guidelines set forth above and comply with the written description requirement. Applicants submit that they have disclosed structural features (e.g., hydrophobic modification appended to specific portions of a polypeptide), extensive discussion of the making and testing of modified polypeptides, and further provides working examples to demonstrate that the structural features adequately describe modified polypeptides. Applicants assert that for the description of a genetic invention to be deemed adequate to describe the genus that the claims encompass requires either

a recitation of the structure of a representative number of members of the genus or a recitation of the common features of the members of the claimed genus. Applicants also assert that in addition to the extensive structural limitations provided in the claims, Applicants describe functional attributes which the modified polypeptides possess.

Applicants' arguments have been fully considered but are not deemed persuasive. The specification and claims have adequately described the hydrophobic modifications. However the written description rejection is based on the protein, and not the modification of the protein. The claims encompass any protein that binds to a receptor that is modified with at least one hydrophobic moiety. There are no common structural features of the claimed proteins; proteins that bind to receptors can have vastly different amino acid sequences, and there is no defining structural characteristic claimed. The claimed proteins also do not have common functional attributes. The recitation of the protein binding to a receptor or coreceptor is not a common functional attribute, because different proteins bind to different receptors and have different effects. The instant specification discloses a single family of proteins (hedgehog) having similar structures, lipid modifications and activities. Given the unpredictability of the effect of hydrophobic modification on proteins and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. There is no structure set forth for the additional sequences, and there is no correlation or nexus provided between possession of a hydrophobic modification and the encompassed functional features of any protein binding a receptor having enhanced biological activity, such

that it is clearly conveyed that possession of any polypeptide having this structural region in common would possess these functional features. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 3-5, 10, 93, 95-97 and 102 remain rejected under 35 U.S.C. 102(b) as being anticipated by Jonassen et al., WO 96/29342, Sept. 26, 1996, for reasons of record in the previous Office Action, Paper No. 14 at pages 11-12 and below.

Applicants traverse the rejection and asserts that Jonassen et al. fails to anticipate each and every element of the claims. Applicants assert that the claims are directed to modification of isolated proteins, and Jonassen et al. only provides for the modification of small peptide hormones, does not teach or suggest that proteins can be modified to achieve any desirable effect, and only provides an invitation to one of skill in the art to attempt such work.

Applicants' arguments have been fully considered but are not deemed persuasive. A small peptide hormone is a protein (see Jonnassen et al., page 2, lines 2-6), and it is a signaling molecule that binds to a receptor. Jonassen et al. teach that proteins can be modified with a lipophilic substituent in the N-terminal amino acid or in the C-terminal amino acid, and that this modification causes a longer half-life in vivo. Jonassen et al. provided at least two working

examples of such modified proteins (see examples 4 and 6) which showed longer half-lives in experiments with animals.

Applicants further assert that the claims require that the modification of the protein does not substantially alter the binding affinity of the protein to its receptor or coreceptor, and Jonassen et al. are completely silent on this issue.

Applicants' arguments have been fully considered but are not deemed persuasive. Although Jonassen et al. do not specifically state that the modification of the protein does not substantially affect binding affinity of the protein to the receptor; however, the purpose of the lipophilic modification is to increase the length of time the protein is in the subject for therapeutic purposes, and to be therapeutically active the modified protein would need to still bind to the receptor. Accordingly, that limitation is inherent to Jonassen's disclosure. Additionally, in the experiment in Example 6, the blood glucose raising effect of glucagon is retained in the modified glucagon but with prolonged action compared to the non-modified glucagon, so that the modified glucagon must have been active and bound to the receptor. It remains that the reference teaches methods/products consistent with the claims. Applicants have not provided fact or evidence to the contrary. Therefore, the rejection is maintained.

It is believed that all pertinent arguments have been answered.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-10, 14, 15, 28-31, 40-42, 46, 48, 66 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over McKay et al., US Patent No. 5,877,309, or Chaikof et al., US Patent No. 6,071,532, in view of Bergsma et al., US Patent No. 5,935,814, Lehninger, Biochemistry, second edition, Worth Publishers, 1970, Wei et al., US Patent No. 5,480,869, Caldwell et al., US Patent No. 5,516,703, Naccache et al. US Patent No. 6,069,128.

Claims 1-10, 14, 15, 28-31, 40-42, 46, 48, 66 and 67 encompass proteins modified with hydrophobic moieties, wherein the protein may be an extracellular signaling protein, the hydrophobic moiety may be at the C-terminal or N-terminal end or internal to the protein and could be appended to or replace an amino acid, the hydrophobic moiety may be a hydrophobic amino acid or protein, a lipid which may be a fatty acid selected from saturated and unsaturated fatty acids having between 2 and 24 carbon atoms, a thioproline group, amide group, maleimide group, acetamide group or thiomorpholine group, wherein the protein further comprises a vesicle in contact with the hydrophobic moiety and may be a cell membrane, micelle or liposome, and wherein the hydrophobic moiety does not substantially affect the binding of the protein to the receptor or coreceptor, and methods of making such proteins.

McKay et al. teach collodial dispersion systems that may be used as delivery vehicles to target the oligonucleotides to a particular organ, tissue or cell type (see column 23, line 64 to column 24 line 67). McKay et al. teaches that such a system could be performed with micelles and liposomes, and provides examples of lipids used in the micelles and liposomes. McKay et al. teaches active targeting, in which a protein (which can be a receptor ligand) can be modified with lipids, which allows insertion of the protein into the lipid bilayer of the micelle or liposome. McKay et al. states:

> In the case of a liposomal targeted delivery system, lipid groups can be incorporated into the lipid bilayer of the liposome in order to maintain the targeting ligand in close association with the lipid bilayer. Various linking groups can be used for joining the lipid chains to the targeting ligand. The targeting ligand, which binds a specific cell surface molecule found predominantly on cells to which delivery of the oligonucleotides of the invention is desired, may be, for example, (1) a hormone, growth factor or a suitable oligopeptide fragment thereof which is **bound by a specific cellular receptor** predominantly expressed by cells to which delivery is desired.

Chaikof et al., US Patent No. 6,071,532, teaches peptide-phospholipid conjugates and methods of making them, in which a protein or peptide is joined to a phospholipid by a flexible spacer arm which serves to optomize peptide bioactivity, in which the conjugate can be incorporated into liposomes and can be used therapeutically to deliver drugs to target cells, wherein the conjugated protein can bind to a receptor (see entire patent). At column 18, lines 20-34, Chaikof et al. state:

> The foregoing disclosure illustrates the various aspects of the invention. These include a composition of matter comprising a lipid-modified saccharide or peptide, including various glycophospholipid and

> peptide-phospholipid conjugates and methods of making and using such compositions. The addition of a phospholipid moiety to an immuno/biologically active saccharide or peptide results in the retention of the immuno/biological activity of the saccharide or peptide while altering the physical properties of the saccharide or peptide to permit its insertion into membrane structures and/or its incorporation into lipid-containing surface coatings in order to convey immuno/biological activity to membranes and surfaces. Such biological activity includes, without limitation, interaction with a cell receptor, promotion of cell adhesion or migration, and the like.

McKay et al. and Chaikof et al. do not teach the specific positions of the modifications in the protein, or some specific hydrophobic modifications besides lipid modification, such as a hydrophobic amino acid.

Bergsma et al., US Patent No. 5,935,814, teaches that it is well known in the art that polypeptides may be modified by techniques known in the art to make them hydrophobic, including variations in amino acid sequence, lipid addition, acylation (to form a thioester) and amidation, and in any combination, and still retain activity. See column 3, line 60 to column 4, line 62). Bergsma et al. state at column 3, line 67 to column 4, line 38:

> "Polypeptides" include amino acid sequences modified either by natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of

modifications. Polypeptides may be branched as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. See, for instance, PROTEINS-STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York, 1993 and Wold, F., Posttranslational Protein Modifications: Perspectives and Prospects, pgs. 1-12 in POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, 1983; Seifter et al., "Analysis for protein modifications and nonprotein cofactors", Meth Enzymol (1990) 182:626-646 and Rattan et al., "Protein Synthesis: Posttranslational Modifications and Aging",Ann NY Acad Sci (1992) 663:48-62.

Bergsma et al. do not teach that the polypeptide may be in a vesicle.

Lehninger teaches that isoleucine is a hydrophobic amino acid (page 72).

Wei et al. teach proteins modified with thioproline (see column, 4 lines 47-50, column 8, line 54 to column 9, line 10 and claim 6).

Caldwell et al. teach proteins modified with maleimide (see column 6, lines 9-28).

Naccache et al. teach proteins modified with acetamide (see column 3, lines 34-46).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to make the hydrophobically modified ligands of McKay et al. or Chaikof et al. that still retain receptor binding activity, by the methods according to Bergsma et al. and including the hydrophobic amino acid isoleucine as taught by Lehninger or thioproline, maleimide or acetamide as taught by Wei et al., Caldwell et al. and Naccache et al., respectively, in order to incorporate the hydrophobically modified ligands into liposomes or micelles containing therapeutic compounds, to target the therapeutic compounds to specific target cells having receptors for the ligands on the surface of the cells. The skilled artisan would be motivated to do so in order to effectively target therapeutic compounds in vesicles to specific types of cells requiring the therapeutic compound, as opposed to a vesicle which would not comprise any specific ligand and would therefore be dispersed generally in a patient, as suggested by McKay et al. and Chaikof et al. There would be a reasonable expectation of success, since the methods of hydrophobically modifying proteins, testing for biological activity and making vesicles were well known in the art at the time the invention was made.

Conclusion

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner